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Reproductive outcome of a case with familial balanced translocation t(3;6): implications for genetic counseling

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ABSTRACT. Although it is known that parental carriers of structural chromosomal rearrangements are associated with recurrent pregnancy loss, subsequent natural pregnancies remain possible. We examined the reproductive outcome of a familial balanced translocation with t(3;6)(q12;q27). Karyotyping of the proband revealed 46,XY chromosomes with the balanced translocation t(3;6). The first 2 pregnancies resulted in spontaneous abortions. Based on the proband karyotype, his father and half-brother were subjected to cytogenetic analysis, and both showed 46,XY, t(3;6)(q12;q27). After genetic counseling, the proband chose to continue the pregnancy. During the third pregnancy, the subject gave birth to a normal male infant. For parental carriers with balanced chromosomal translocations, natural pregnancy should be considered during genetic counseling.

Key words: Assisted reproduction treatment; Genetic counseling; Familial balanced translocation; Reproductive outcome

INTRODUCTION

A reduced ability to conceive and deliver a healthy offspring can be caused by various factors. Among them, the presence of balanced chromosomal translocation in karyotype has been observed in 0.6% of infertile couples and in as many as 9.2% of couples with recurrent miscarriages (Vozdova et al., 2012). Reciprocal translocation is defined as the exchange of chromosomal material between the arms of 2 heterologous chromosomes, thus changing the order but typically not the amount of genetic material. Carriers of balanced chromosomal translocations may have all of the necessary genetic information for normal development. Balanced translocations can be transmitted through generations; it is assumed that most familial cases are phenotypically normal, resulting from balanced rearrangements (Kim et al., 2011). However, when one member of a couple carries a balanced chromosome translocation, the risk of miscarriage is approximately doubled (Kavalier, 2005). Individuals with balanced reciprocal translocations are known to have high rates of unbalanced gametes, exhibit impaired or reduced gametogenesis, produce large numbers of unbalanced embryos, and have a greater chance of being infertile and/or a high risk of conceiving chromosomally abnormal pregnancies that lead to recurrent spontaneous abortions or children with congenital anomalies (Fischer et al., 2010; Fiorentino et al., 2011; Mokánszki et al., 2012).

Previous studies of carriers of balanced chromosomal translocations with recurrent spontaneous abortions (Beyazyurek et al., 2010; Simpson, 2012) showed that preimplantation genetic diagnosis (PGD) for translocations reduced loss rates from >90 to <15%. The *in vitro* fertilization method accompanied by PGD increases the chance of translocation carriers fathering a healthy child (Vozdova et al., 2011). However, there are some risks associated with assisted reproduction treatment. Recently, experts reached a consensus regarding the reasons for potential differences in outcomes between assisted-conception and naturally conceived children in the Sixth Evian Annual Reproduction (EVAR) Workshop Group Meeting. *In vitro* fertilization-conceived children have lower birth weights and higher peripheral fat, blood pressure, and fasting glucose concentrations than controls. Women undergoing assisted reproduction are often older, which increases the chance of obtaining abnormal gametes; this may result in deviations in outcomes between assisted-conception and naturally conceived children (Fausera et al., 2014).

In addition, despite the known association of parental carriers of structural chromosomal rearrangements and a history of recurrent pregnancy loss, subsequent natural pregnancies remain possible. Several studies have reported that the success rates of subsequent natural pregnancies in couples and translocations after appropriate treatments ranged from 30-70% (Ozawa et al., 2008). Recently, Kochhar and Ghosh (2013) reported that the risk of having a chromosomal aberration was not related to the number of previous miscarriages. Over the next 2 years, two-thirds of the 49 documented pregnancies resulted in a normal live birth, while one-third miscarried. Franssen et al. (2006) documented a live birth rate of 83% among carrier couples after a mean follow-up of 5.8 years. Thus, natural conception or assisted reproduction treatment should be examined for carriers of balanced chromosomal translocations. In the present study, we report the reproductive outcome of a family with balanced translocation 46,XY, t(3;6)(q12;q27) and review of the literature.

MATERIAL AND METHODS

Patients

A 31-year-old man was referred for genetic counseling because his wife's first 2 preg-

nancies had resulted in spontaneous abortions during their first trimesters. He was an office worker who was 178 cm in height. His wife was 29 years old, a teacher, and 158 cm in height. They were in a non-consanguineous marriage. There was no family history of miscarriage, congenital anomalies, or infertility determined from either the husband or the wife. No abnormal symptoms were detected, and physical examination revealed that the couple was phenotypically normal. No evidence of uterine abnormalities or other diseases was detected during pregnancy. Cytogenetic analysis was performed on peripheral blood lymphocytes of the couple. The proband's karyotype was 46,XY chromosomes with a balanced translocation t(3;6). His wife had a normal female karyotype. Based on the abnormal karyotype of the proband, his father and half-brother underwent cytogenetic analysis. The results were 46,XY, t(3;6)(q12;q27) for both subjects. The half-brother was unmarried and 180 cm in height. Physical examination showed that the half-brother was phenotypically normal. His father stated that his wife did not have a history of miscarriage. The proband's doctor suggested that they continue the pregnancy, to which the couple agreed. During the third pregnancy, an amniocentesis conducted at 16 weeks revealed that the karyotype was 46,XY, t(3;6)(q12;q27). The child was born as a phenotypically normal male.

Cytogenetic analysis

G-banding was performed using cultured peripheral blood lymphocytes (Zhang et al., 2013). After a 72-h incubation period, lymphocytes were cultured in RPMI-1640 (GIBCO, Grand Island, NY, USA), phytohemagglutinin (Yihua Medical Technology, Shanghai, China), and fetal bovine serum (Dingguo Biotechnology, Beijing, China), followed by treatment with colcemid. G-banding of chromosomes in metaphase was then performed. At least 20 metaphases were analyzed per patient. Chromosomal abnormalities were described according to the International System for Human Cytogenetic Nomenclature (2009).

RESULTS

A G-band karyogram of the proband revealed a balanced translocation between chromosomes 3 and 6 (Figure 1a). His father and half-brother were similar to that of the proband. Derivative 3;6 chromosome and chromosome ideograms of 3;6 translocation are shown in Figure 1b and c. Figure 2 shows the pedigree of the family with balanced translocation t(3;6)(q12;q27).

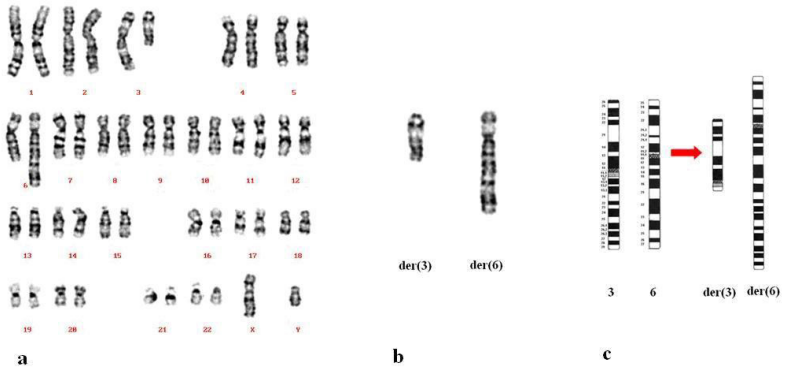

Figure 1. a. GTG; **b.** derivative 3;6 chromosome; **c.** ideogram of 3;6 translocation.

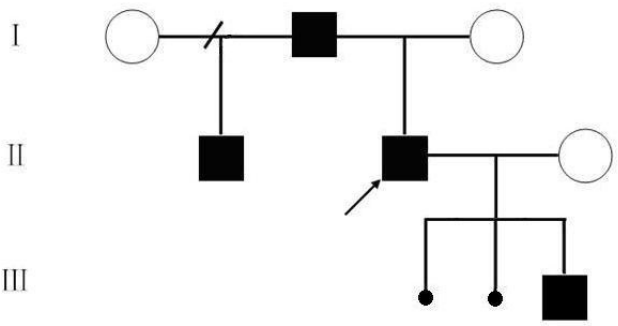

Figure 2. The pedigree of the family with balanced translocation t(3;6).

DISCUSSION

Balanced translocation carriers account for 0.08-0.3% of the normal population (Kochhar and Ghosh, 2013). The carrier status of balanced translocation is associated with recurrent miscarriage. An apparently balanced translocation may produce a clinical phenotype by gene disruption or altered expression of genes in or around the breakpoint region (Sobreira et al., 2011). Three hypotheses have been proposed to explain such phenotype abnormalities, including a break in a gene, positional effect, and cryptic deletion or duplication (Callier et al., 2007). A gene (or genes) may have been disrupted by breaks and offspring were homozygous for a recessive gene mutation, masked by the parents who were heterozygous carriers (Beyazyurek et al., 2010). However, some studies have reported that the reproductive outcomes of balanced translocation carriers with recurrent pregnancy loss (RPL) were live births (Goddijn et al., 2004; Kochhar and Ghosh, 2013). In this study, we report the reproductive outcome of a case with familial balanced translocation t(3;6). As shown in Figure 2, the proband's father was a carrier of a balanced chromosomal translocation. His 2 sons exhibited balanced reciprocal translocations. Additionally, the proband's child was born a phenotypically normal male in the third pregnancy after 2 consecutive miscarriages.

Carriers of completely balanced chromosomal translocations possess all necessary genetic information. Individuals with balanced reciprocal translocations are clinically normal, and reciprocal translocations can be inherited (Keify et al., 2012). However, most studies (Ozawa et al., 2008; Farra et al., 2011) have reported an increased risk of having progeny with unbalanced karyotypes with interference in the meiotic segregation of abnormal chromosomes, which can cause miscarriage or stillbirth. Additionally, some researchers have reported that in couples with RPL, the number of female carriers with balanced chromosomal aberrations significantly exceeded that of males. A possible cause contributing to a higher incidence of female translocation carriers is that only 1 ovum matures each month in female carriers (Soh et al., 1984; Kochhar and Ghosh, 2013). However, male carriers release millions of sperm in each ejaculation. The patients were familial male translocation carriers in our study.

Sperm segregation studies report ranges of normal/balanced gametes from 19-81%. Because of this variability, it has been assumed that the proportion of normal/balanced gametes produced is specific in each case (Anton et al., 2008). When gametes with an unbalanced translocation are present, they will infrequently fertilize the ovum to produce abnormal zy-

gotes. Hence, determining the frequency of unbalanced gametes can help to establish a reproductive prognosis in individual cases and provide a reasonable assessment of the chances of having a normal or balanced embryo (Vozdova et al., 2008). Vozdova et al. (2008) reported that the incidence of chromosomally unbalanced or aneuploid gametes varies in individual translocation carriers, even if the same chromosomes are included in the translocation. Therefore, the live birth rate should be higher for male balanced translocation carriers.

Assisted reproduction treatment may be considered as an option for achieving a healthy birth for couples with recurrent miscarriages. The *in vitro* fertilization method accompanied by PGD reduces recurrent spontaneous abortions and increases the pregnancy success rate (Chang et al., 2012; Keify et al., 2012). Scriven et al. (2013) reported that PGD can reduce the risk of miscarriage to the level found in the general population, and that PGD benefits couples with high-risk translocations. Other studies have reported successful birth after PGD for couples carrying an identical balanced reciprocal translocation (Wiland et al., 2008; Mackie et al., 2010; Beyazyurek et al., 2010). However, there are also risks associated with assisted reproduction treatment. *In vitro* fertilization-conceived children have lower birthweights and higher peripheral fat, blood pressure, and fasting glucose concentrations than controls. Women undergoing assisted reproduction are often older, which increases the chances of obtaining abnormal gametes that may cause deviations in outcomes between assisted-conception and naturally conceived children (Fausera et al., 2014).

Recently, studies reported that the carriers of balanced translocations with RPL have higher live birth rates. Kochhar and Ghosh (2013) reported that nearly two-thirds of couples in which 1 partner is the carrier of balanced translocation are likely to have a normal outcome in subsequent pregnancy. A total of 30/43 documented pregnancies (70%), among carriers of balanced translocations with RPL, were live births (Goddijn et al., 2004). Franssen et al. (2006) reported a live birth rate of 83% among carrier couples after a mean follow-up of 5.8 years.

Chromosome 3 and 6 reciprocal translations reported in previous studies are shown in Table 1. The balanced translocations can be familial. Our patient had an uncommon t(3;6)(q12;q27) karyotype. This is the first report of this karyotype. Scriven et al. (2013) concluded that for fertile carriers of translocations with a low risk of conceiving a chromosomally unbalanced offspring, natural conception may be a more viable option.

Table 1. Comparison of familial balanced translocation t(3;6).

Karyotype	Origin	References
t(3;6)(q12;q15)	Familial	Eleveld et al., 2001
t(3;6)	Familial	van den Berg et al., 1995
t(3;6)(p12.3;q24.3)	Familial	Yusenko et al., 2010
t(3;6)(p14;p11)	Familial	Smith et al., 1993
t(3;6)(p14;p11)	Familial	Markkanen et al., 1987

These studies provide a better understanding of the reproductive consequences for carriers of balanced translocation and should be useful in prenatal diagnosis and genetic counseling.

CONCLUSIONS

In summary, parental carrier with balanced chromosomal translocations can be trans-

mitted through generations. Individuals with balanced reciprocal translocations are known to have a high risk of conceiving chromosomally abnormal pregnancies that lead to recurrent spontaneous abortions. Assisted reproduction treatment may be considered as an option for achieving a healthy birth for couples with recurrent miscarriages. Natural conception should be considered as a part of genetic counseling for carriers of balanced chromosomal translocations, particularly for male carriers.

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